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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,104	02/11/2004	Dirk Kostrewa	13232 US2 (C038435/012842)	2828
7590	02/10/2005		EXAMINER	
Stephen M. Haracz, Esq. BRYAN CAVE LLP 1290 Avenue of the Americas New York, NY 10104-3300			SAIDHA, TEKCHAND	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/776,104	Applicant(s) KOSTREWA ET AL.	
	Examiner Tekchand Saidha	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 February 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☒ Certified copies of the priority documents have been received in Application No. 09/044,718
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The Preliminary Amendment filed February 11, 2004 is acknowledged. Claims 12-24 have been canceled as the preliminary amendment. Claims 1-11 are pending and under consideration in this examination.

2. ***Continuation of prior application***

When a non-provisional application claims the benefit under 35 USC 120 of a prior application(s), the first sentence of the specification should read, e.g., "This application is a continuation/divisional of U.S. Application No. 10/-----, filed....., now US Patent....., which application is a continuation/divisional No. 09/-----, filed, now US Patent....." . Inclusion of the missing information is required.

3. ***Priority***

Acknowledgment is made of applicants' claim for priority based on an application filed at the EPO on March 25, 1997.

4. ***Specification***

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

5. ***35 U.S.C. § 112, first paragraph (Written Description)***

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1-11 are directed to a process for the production of a modified phytase having a desired property improved over the property of the corresponding unmodified phytase by determining (1a) three dimensional structure of any unmodified phytase, (2a) three dimensional structure of any

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second phytase which has the desired property, and (3a) three dimensional structure of a third phytase of *Aspergillus niger* used as a template based on the alignment to determine said three dimensional structures; (1b) based upon the 3-D structures obtained from 1a-3a, determine the amino acids of the active site of the unidentified phytase and of the second phytase having the desired property which active site provides to identify positions to be modified by obtaining and modifying the DNA sequence in order to modify the active site which provides the desired property in the unmodified phytase; further integrating the modified DNA into a vector and a host cell.

The specification, however, only provides a single representative species of modifying *Aspergillus fumigatus* for improving the specific activity based upon the 3-D structure and amino acid correspondence of *Aspergillus niger* of SEQ ID NO : 1, at positions 27, 66, 140, 205, 274, 277, 282 & 340 and further including one or more mutational modification. There is no disclosure of any particular structure to function/activity relationship in the single disclosed phytase species to other phytase species where such sequences are conserved in order to establish a relationship among species or modify the enzyme to have any desired property such as for example, a broader pH profile, increased thermostability, etc. The specification also fails to describe additional representative species of these phytases by way of 3-D structures which can be modeled using the 3-D structure of *Aspergillus niger* as the template which may then be used for modifying any unmodified phytase irrespective of their homology to the template, and to any desired property. No identifying structural characteristics are described for these other than the properties or activity recited in claims, for which no predictability of structure is apparent. Given this lack of additional representative species, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

6. ***Claim Rejections - 35 USC § 112, first paragraph (Enablement)***

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method (or process) of modeling the production of a modified *Aspergillus fumigatus* phytase having the potential for improving a desired enzymatic property by determining (1a) three dimensional structure of any unmodified phytase, (2a) three dimensional structure of any second phytase which has the desired property, and (3a) three dimensional structure of a third phytase of *Aspergillus niger* used as a template based on the alignment to determine said three dimensional structures; (1b) based upon the 3-D structures obtained from 1a-3a, determine the amino acids of the active site of the unidentified phytase and of the second phytase having the desired property which active site provides to identify positions to be modified by obtaining and modifying the DNA sequence in order to modify the active site which provides the desired property in the unmodified phytase; further integrating the modified DNA into a vector and a host cell, does not reasonably provide enablement for modifying any phytase having any desired property based upon the steps a-e of claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) [*Ex parte* Forman [230 USPQ 546 (Bd. Pat. App. & Int. 1986)]]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim. The factors most relevant to this rejection are [the scope of the claims, unpredictability in the

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art, the amount of direction or guidance presented, and the amount of experimentation necessary].

The specification provides a single example of modifying *Aspergillus fumigatus* for improving the specific activity based upon the 3-D structure and amino acid correspondence of *Aspergillus niger* of SEQ ID NO : 1, at positions 27, 66, 140, 205, 274, 277, 282 & 340 and further including one or more mutational modification. Since, Applicants' process claims relies upon 3-D structure modeling of numerous phytases based upon known 3-D structure of *Aspergillus niger* it is important to assess the comparative molecular modeling of tertiary structures of proteins. Mosimann et al. [Proteins: Structure, Function & Genetics, 23 :301-317 (1995)] analyzes the current state of comparative molecular modeling of tertiary structures of proteins, and shows that where sequence identity between the target and the template is high (>70%) comparative molecular modeling is highly successful. Based upon their detailed analysis it could be inferred that the quality of the model 3-D structure is dependent upon the closeness of the sequence homology, and which would otherwise lead to developing 3-D models that are unpredictable if relied upon for modifying a given protein or enzyme or a phytase.

The 'phytase' also called 'acid phosphatase'. As can be seen from the enclosed sequence search alignment [see page 4, result 4], Applicants' SEQ ID NO: 1 [*Aspergillus niger*] is 16.5% identical to an acid phosphatase [or phytase/Accession No. P24031] from yeast. Similarly a number of phytases from diverse microorganisms display a range of sequence homologies between target and the template [*Aspergillus niger*] insufficient to provide a quality model of the 3-D structure and unreliable for using it in a process for the production of modifying any phytase. Additional unpredictability in the method is due to modifying any phytase for a desired property, which may be, for example, high specific activity, broader pH profile, thermostability, etc., and

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must be optimized for the diverse phytases, which without sufficient guidance will lead to unpredictability.

The specification does not support the broad scope of the claims which encompass a method (or process) for the production of a modified phytase, because the specification does **not** establish: (A) optimization of diverse range of phytases 3-D structure(s) or modeling of phytases 3-D structures, of varying homologies, which may be used in the modification of any phytase; (B) the general tolerance of the phytases of (a) to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any phytase residues with an expectation of modifying the desired biological function or property; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, developing such a process for the production of a modified phytase having the desired property is unpredictable and the experimentation left to those skilled in the art is improper, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571)

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272 0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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February 3, 2005